Deep Learning Techniques for Automatic Classification and Analysis of Human in Vitro Fertilized (IVF) embryos.

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***Abstract.*Automated classification of human In Vitro Fertilized (IVF) embryos using Convolution Neural Networks is presented in the paper. Embryos comprise smaller radii cell structures and get differentiated quickly in early days after fertilization, making it difficult to algorithmically track and identify viability of embryo. Machine learning algorithms are yielding better results than alternate methods like Hugh's circle transforms and modified vesselness filters. The method is useful in increasing the implantation efficiency.**

Keywords: In vitro fertilization, Machine Learning, Convolution Neural Networks, Cloud Services

I. INTRODUCTION

Recognizing viability of human embryos from microscopic images is an extremely tedious process that is susceptible to error and subject to intra- and inter-individual unpredictability [1,2]. Automating classification of these embryo images will have the benefit of reducing time and cost, minimizing errors, and improving outcome, consistency of results between individuals and clinics. Several techniques have been discussed in literature to ease the process of automation taking into consideration of day2 as well as day3 embryo images. However, grading the embryos based on the cell division, size of the cell and the fragments present becomes difficult because of constraints in the imaging process. Like, the exposure time (embryos are sensitive to the temperature), the light intensity variation and the transparency of the specimen all cause variations in the image. Embryo quality assessment based on Blastomere circle and grading do not yield sufficiently reliable classification.

Convolutional Neural networks (CNNs) are a type of deep learning models that can act directly on the raw inputs, thus automating the process of feature construction. Machine learning algorithms are proving to be better in checking viability ofembryo and prediction of the outcome of implantation.

The convolutional neural network APIs used for the recognition of microscopic images will detect growth and grading is done based on the previous trained dataset. Also this framework will allow us to automatically classifyand grade the human embryos based on the previous. The framework employs a deep convolutional neural network model trained to count cells from raw microscopy images. Here we exhibit the effectiveness of proposed approach on a data set of 350 human embryos. The results depict that the deep CNN APIs will provide strongassessmentson the training precision of about 87.5 % and recall is 86% for the embryos of initial, day1, day2, day3 and day5.

(a) (b) (c) (d) (e)

Fig.1. Examples of developing embryos: (a) one-cell stage, (b) two-cell stage, (c) three cell stage, (d) four-cell stage and (e) 5-or-more cell stage.

(a) (b) (c) (d) (e)

Fig.2. stages of embryo development: (a) initial stage, (b) day 1, (c) day 2, (d) day 3, and (e). day 4

The intensity variation between the cell and boundaries will reduce quality and result in faint cell boundaries. Classification and analysis of these human embryos cells makes it challenging by the fact that the cells exhibit variability in their appearance, size and shape. Also, each embryo grows (cells undergo divisions) in a compact manner where cells severely overlap with each e.g., dividing cells. Here, we focus on the literature related to human embryo image analysis. other. Moreover, cells are surrounded by distracting noise such as extra cellular material (fragments) attached to the growing embryo and surrounding gel material (see Fig. 1 and Fig. 2 (a)–(e) for examples). All these difficulties make hand crafted algorithms for automated cell counting fragile.

Here in this paper, the network is trained using the preprocessed microscopic images, we utilize the APIs to test the images using convolutional neural network (CNN). The datasets are initially trained with respect to day1 images, than with day2, day3 and day5. The available features of the embryos will give the precise grading and the size of the blastomere. When these images are fed to the neural network the precision and recall is better, the system is able to recognize and validate whether the selected embryo grade based on previous training. Our goal is to automatically count the number of cells in the developing embryos up to the 5-cell stage (with higher cardinality being grouped into a "5-or-more" category). We do so using a convolutional neural network (CNN) that can learn from vast amount of training data to overcome the difficulties presented above.

II. Related work:

Human embryo detection, cell detection, segmentation, and tracking are well-studied problems in computer vision. Most of the research work has been done in developing techniques to deal with the difficulties that generally occur such as deformable objects, groups of moving objects, missing data, and occlusions [2, 3]. However, the combination of these complexities within a single application presents significant difficulties, which is the case for many of the medical image analysis tasks. These difficulties are even more acute in the context of cell images, which are often noisy, feature-poor, and undergoing topology changes, Human embryo development is more fragile than many other species [5]. The automation of human embryonic cell monitoring, in addition to above-mentioned difficulties, is further challenged by the fact that development varies substantially betweenembryoswithadifferent daysandthatembryosexhibitawiderangeof behavior during cell divisions. Also, in many cases embryo morphology varies within a cell stage and conforms between cell stages (for example, for 4-cell cases see Fig. 2 (a)–(e)). This variability makes it difficult to design feature descriptors that could reliably express the information we want to obtain from the images under analysis. Human embryonic cell analysis is non-invasive, which makes these techniques not appropriate.In practice, however, and in particular in the case of human embryos, the images background contains a lot of noise, such as fragments, and the cells of the growing embryo greatly overlap each other.

In this paper, we therefore address the cell automation problem and grading which is challenging scenario. As to this end, we introduce a CNN-based counting approach that requires minimal annotations, i.e., only the number of cell in each image. Additionally, trained sequence of images fed to the CNN network which intern smoothes the individual CNN predictions across the entire sequence. Our resultsdepicts that our approach outperforms, by a large margin, the Tensor flow method on the challenging task of counting cells in early stage human embryo development.

III. Convolutional Neural Network

Aconvolutional neural network (CNN or ConvNet) is a type of feed-forward artificial neural network made up of neurons that have learnable weights and biases, very similar to ordinary multi-layer perceptron (MLP) networks. The CNNs take advantage of the spatial nature of the data. In nature, we perceive different objects by their shapes, size and colors. These primitives are often identified using different detectors (e.g., edge detection, color detector) or combination of detectors interacting to facilitate image interpretation (object classification, region of interest detection, scene description etc.) in real world vision related tasks. These detectors are also known as filters. Convolution is a mathematical operator that takes an image and a filter as input and produces a filtered output (representing say edges, corners, colors etc in the input image). Historically, these filters are a set of weights that were often hand crafted or modeled with mathematical functions. The filter outputs are mapped through non-linear activation functions mimicking human brain cells called neurons.Convolutional networks provide a machinery to learn these filters from the data directly instead of explicit mathematical models and have been found to be superior (in real world tasks) compared to historically crafted

filters. With convolutional networks, the focus is on learning the filter weights instead of learning individually fully connected pair-wise (between inputs and outputs) weights. In this way, the number of weights to learn is reduced when compared with the traditional MLP networks from the previous tutorials. In a convolutional network, one learns several filters ranging from few single digits to few thousands depending on the network complexity.

We have successfully compared the results if both i.e. Vesselness Filtered algorithm and CNNs algorithm. The CNN algorithm is giving a better result for the grading of embryos and mapping the circles in case of blastomeres. Further different days of the cells is clearly identified by the trained network, with respect to radius, number of cell division i.e 2 PN, 2-cell, 4-cell, 8-cell etc. A carefully-designed RESTful web API defines the resources, relationships, and navigation schemes that are accessible and implementable to client applications. When we implement and deploy this web API, we are considering the requirements of the embryo features such as size of the blastomere, division, radius of all cells, alignment, grades, day of cell and the way in which the web API is been developed for our data. The implementation considers the data fed to the neural network and focusses on best practices available in order to train the system so as to grade them automatically

IV. Deep Learning Techniques:

Microsoft Azure APIs for the classification of human IVF images:

Custom Vision Service is a tool for construction of custom image classifiers. It makes it easy and fast to build, deploy, and improve an image classifier. Here Microsoft provides a REST API and a web interface to upload your images and train. RESTFUL API's are machine learning system that operates at large scale and in heterogeneous environments. Custom vision services use dataflow graphs to represent computation, shared state, and the operations that mutate that state. It maps the nodes of a dataflow graph across many machines in a cluster, and within a machine across multiple computational devices, including multicore CPUs, general purpose GPUs, and custom-designed ASICs. Custom Vision Service accepts training images in JPG/JPEG, PNG, and BMP format, up to 6 MB per image (prediction images can be up to 4 MB per image). Images are recommended to be 256 pixels on the shortest edge. Any images shorter than 256 pixels on the shortest edge will be scaled up by Custom Vision Service. Trained images are assigned with tags based on the features which are selected to the embryos.

These tags will be the embryo day, radius, grade as measured by the previous algorithm. Embryo features which are to be considered for the training sequences, then uploaded to train the network. The CNN will take some time to train because the images are large and high number. The evaluation of this trained system is validated by the use of precision and recall indicators. Custom Vision Service uses K-fold cross validation for training the set of images given to the network and to calculate the percentage of precision, recall. The precision and recall indicators will tell how good the classifier is, based on automatic testing, so that the network can be retrained to improve the precision

Fig 3: Precision and recall percentage

Note: Each time we hit the "Train" button, we will create a new iteration of the trained classifier. It is possible to view all old iterations in the Performance tab, and we can delete any that may be obsolete.

The classifier uses all the images to create a model that identifies each tag. To test the quality of the model, the classifier then tries each image on its model to see what the model finds.

After the training is completed we can test any of the embryo image using the **Quick Test,** here the image is uploaded to test the classifier, if the trainingis good then the test results will identify the day, grade and the percentage of precision for a particular embryo.

Feature Extraction:

Convolutional Neural Network which is trained using different tags represents the features of the human embryos. The feature will be supplied to the network while training, so that the precision of the system is 100%. Normal embryo images as well as abnormal images are considered for training the network. The features such as radius of the cell, division whether it is day-2, day-3, day-4 or Day-5 will be identified based on these features.

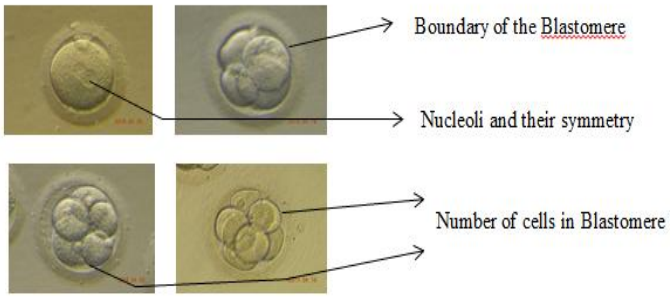


Fig 4: Features to be extracted from embryos i.e day, cell division, radius of cell.

Classification:

This work uses an ensemble of neural network to perform the classification task. A convolutional neural is a layered network of simple processing elements connected together to form a network of nodes that uses a mathematical model for information processing. Different neural network classifiers can be obtained by varying the network architecture and the choice of the algorithm designed to infer the strength (weights) of the connections in the network to produce a desired signal flow. The network can also be trained for the more number of sample images so as to train the classifier efficiently.

Statistical Analysis:

The accuracy of the classifier depends on how well the network is trained and is it separates the group of images being tested (embryos) into the four classesi.e D1, D2, D3, D4 so as to have the healthy birth of the child. Accuracy is measured by the frequency of the cells being identified by the software and using the result obtained by the embryologists. A rough measurement of the images graded for the respective days is as show below.

In these 500 samples of embryo images, each of Day1, Day2, Day3, Day4 and Day5 there are totally 700 blastomeres and almost all the cells detected were true cells. Among them, except a few (15 cells) cells all other cells are correct detections.

Here, we define true positive (TP) as the correct detection, false alarm/false positive (FP) as the detected circle/ellipses which are not correspond to any real cell, misdetection/false negative (FN) as the real cells that are not detected. Afterwards, the precision and recall are again used to measure the performance.

The total precision for all Blastomere is 0.9172. This means for a given detection, the probability that it is correct detection is 0.9172. The total recall is 0.9332, which means for a given real cell, the probability that it will be correctly detected is 0.9332.
The average precision is 0.8755, which means the average for the precisions of all embryo images. Similarly, the average recall is 0.7562.

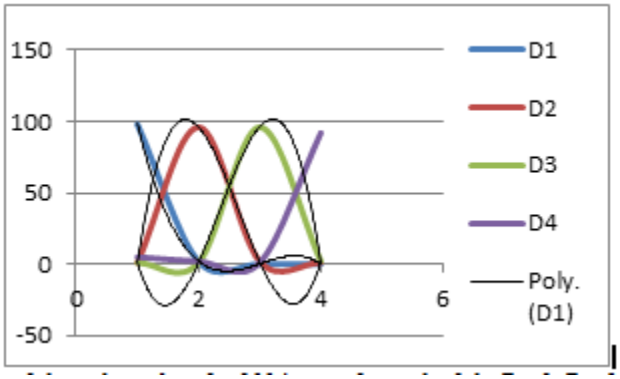


Fig5: Analysis of the embryo data for 100 images for each of the Day1, Day2, Day3, Day4.

Unpaired *t* test results:

P value and statistical significance:
The two-tailed P value is less than 0.0001 by conventional criteria; this difference is considered to be extremely statistically significant.

Confidence interval:
The mean of Group One minus Group Two equals -0.92
95% confidence interval of this difference: From -0.98 to -0.87

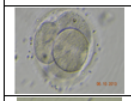
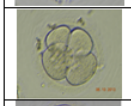
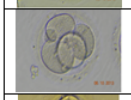
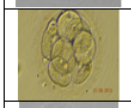
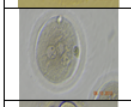
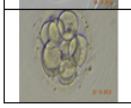
Intermediate values used in calculations:
t = 35.5106
df = 208
standard error of difference = 0.026

V. RESULTS:

Using Custom Vision APIs the system is been trained with sufficient number of embryo images related to day1, day2, day3 and day5 with parameters like shape, cell division and size. Initially all the normal images are taken to train the system i.e the images without the fragmentation. Initial period all the embryo images were taken and trained, here the recall rate is 89.2% and the precision is 85.7%.

It is clearly understood that the response is better in the training period. The images are tagged according to the days and grades, once this is done further any embryo image taken for the quick test and the observation results were good enough to classify these images as grade1, grade2, grade3, grade4, grade5. Some of the performance results tested are shown below.

Table 1 :Automated Embryo Classification Results

Image	Initial	D1	D2	D3	D5	Grade
	98%	0%	53.2%	98%	14.2%	99%
	99%	0%	99.9%	18.4%	40.4%	99.9%
	99.9%	0%	98.6%	42%	2.2%	98.2%
	99.9%	0%	0%	99.9%	8.3%	96%
	99.9%	99.9%	0%	0%	0%	99.9%
	99.9%	0%	0%	10.4%	99.9%	98%

VI. DISCUSSION:

The paper presented focuses on new techniques for human embryo image classification based on a training sequence for the convolutional neural network system. The results clearly depicts as to how the APIs used to classify these embryos and are encouraging, in particular considering that they have been obtained using a 'small' training set with very few positive samples. For pronucleated (initial stage of embryo development) oocytes and embryos, it is probable that other type of descriptors not specifically designed for prevalent textural images might be used. In fact, the alignment and the number of nucleoli or the number and size of blastomeres are not textural features. Certainly time lapse imaging technique is a significant advantage over a static assessment scheme but it does not necessarily rule out the possibility of adding valuable information coming from large databases of stored images especially when used with new technologies such as pattern recognition and artificial intelligence techniques. The two possibilities (dynamic and static observation) might be used together and integrated in a more thorough analysis for practical aims in a normal IVF clinical setting.

An important application for the selection of viable embryo might be the optimization of the cryopreservation strategy and the avoidance of embryo selection in countries where it is not permitted. The most practical and original perspective of this study is the possibility of obtaining a reliable method to help physicians and biologists in selecting embryos or oocytes. This study group is planning to test the proposed method on a larger data set, using an automated segmentation procedure and to combine the information coming from the oocytes, pronuclei and embryos. The proposed approach might become a tool shared among several IVF laboratories for objective, automatic and non-invasive oocyte or embryo assessment.

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